Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for chlormadinone, the scientific conclusions are as follows:

During this reporting period a signal on anxiety and depression has been evaluated by one MAH following a request from the French authority.

Following detailed assessment of the cases retrieved on anxiety and depression with several cases where possible causality is reasonable including a positive dechallenge for depression in two cases and for anxiety in one case and taking into account the listedness of these adverse reactions in the product information of other progestin only medicinal products, the lead member state considers that anxiety and depression should be included as adverse reactions in section 4.8 of the SmPC and section 4 of the PL together with a corresponding warning and advice for physicians and patients in the respective sections of the SmPC and PL.

With regards to venous thrombosis and thromboembolic events a review performed by one MAH did not show a clear causal relationship between the cases of thrombosis and chlormadinone acetate use. Most of the 51 cases identified had confounding factors or concomitant diseases. In addition, in 15 cases concomitant treatments were identified which may be confounding factors. In 7 cases without confounding factors information given was very limited. Since also the role of progestagens in the development of thromboembolic events is still under discussion in the international scientific community the lead Member state agreed with the MAH that this issue is still an important potential risk. Since the current warning statement included on this important potential risk states that no cases have yet been reported, a revision of this statement is considered warranted.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for chlormadinone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing chlormadinone is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing chlormadinone are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning on thromboembolic events should be revised/added as follows:

"**Cases of thromboembolic events have been reported in patients under oral chlormadinone monotherapy.**

The prescription of this medication should be carefully considered in patients with medical history of thromboembolic events or in the presence of risk factors."

A warning on depression and anxiety should be added as follows:

"**Anxiety and depression are known side effects for progestins and cases have also been reported under oral chlormadinone monotherapy (see section 4.8). Patients should be advised to contact their doctor in case of appearance or aggravation of symptoms for depression, anxiety, or mood disorders.**"

- Section 4.8

The following adverse reaction(s) should be added under the SOC Psychiatric disorders with a frequency not known:

- depression

- anxiety

The following adverse reaction(s) should be added under the SOC Vascular disorders with a frequency not known

- thromboembolic events

Package Leaflet

The following warnings should be added under Section 2 subheading "Tell your doctor if any of the following conditions apply to you":

"**Contact your doctor if you suffer from anxiety or depression or if mood disorders including anxiety and depression appear or are becoming worse during treatment with chlormadinone.**"

"Tell your doctor if you have a history of blood clots in a vessel of your legs, lungs or other organs or if you suffer from other risk factors (such as hypertension, high weight/obesity, and smoking) since in these cases the use of chlormadinone may need to be carefully considered.

There have been cases reported of blood clots (thromboembolic events) when using chlormadinone (CMA).”

Section 4

The following adverse reaction(s) should be added with a frequency not known:

- **depression, anxiety**

- Blood clots in a vessel (thromboembolic events) (frequency not known)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 October 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 December 2017